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(54) Title: METHODS FOR TREATING GENETICALLY-DEFINED PROLIFERATIVE DISORDERS WITH HSP90 INHIBITORS

| Type of Aberration | Background Literature | Affected Gene(s) | Protein Domain | Fusion Protein | Disease |
|---|---|---|---|---|---|
| t(9; 22)(q34; q11) | de Klein, A. et al. Nature 300, 765-767 (1982) | *CABL* (9q34)<br>*BCR* (22q11) | tyrosine kinase<br>serine kinase | serine + tyrosine kinase | CML/ALL |
| inv14 (q11; q32) | Baer, R., Chen, K.-C., Smith, S. D. & Rabbitts, T. H. Cell 43, 705-713 (1985); Denny, C. T. et al. Nature 320, 549-551 (1986) | TCR-α (14q11)<br>VH-(14q32) | TCR-Cα<br>Ig VH | VH-TCR-Cα | T/B-cell lymphoma |
| t(1; 19)(q23; p13.3) | Kamps, M. P., Murre., C., Sun, X.-H. & Baltimore, D. Cell 60, 547-555 (1990); Nourse, J. et al. Cell 60, 535-545 (1990) | *PBX1* (1q23)<br>*E2A* (19p13.3) | HD<br>AD-b-HLH | AD + HD | pre-B-ALL |
| t(17; 19)(q22; p13) | Hunger, S. P., Ohyashiki, K. Toyama, K. & Clearly, M. L. Genes Dev. 6, 1608-1620 (1992); Inaba, T. et al. Science 257, 531-534 (1992) | *HLF* (17q22)<br>*E2A* (19p13) | bZIP<br>AD-b-HLH | AD + bZIP | pro-B-ALL |
| t(15; 17)(q21-q11-22) | Giliard, E. F. & Solomon, E. Sem. Cancer Biol. 4, 359-368 (1993) | *PML* (15Q21)<br>*RARA* (17q21) | Zinc-finger<br>Retinoic acid receptor-α | Zinc-finger + RAR DNA and ligand binding | APL |
| t(11; 17)(q23; q21.1) | Chen, Z. et al. EMBO J. 12, 1161-1167 (1993) | *PLZF* (11q23)<br>*RARA* (17q21) | Zinc-finger<br>Retinoic acid receptorα | Zn-finger + RAR DNA and ligand binding | APL |
| t(4; 11)(q21; q23) | Djabali, M. et al. Nature Genet. 2, 113-118 (1992); Gu, Y. et al. Cell 71, 701-708 (1992) | *MLL* (11q23)<br>*AF4* (4q21) | A-T hook/Zn-finger<br>Ser-Pro rich | A-T hook + (Ser-pro) | ALL/preB-ALL/ ANLL |
| t(9; 11)(q21; q23) | Nakamura, T. et al. Proc. natn. Acad. Sci. U.S.A. 90, 4631-4635 (1993); Lida, S. et al. Oncogene 8, 3085-3092 (1993) | *MLL* (11q23)<br>*AF9/MLLT3* (9p22) | A-T hook/Zn-finger<br>Ser-Pro rich | A-T hook + (Ser-Pro) | ALL/preB-ALL/ ANLL |
| t(11; 19)(q23; p13) | Tkachuk, D. C., Kohler, S. & Cleary, M. L. Cell 71, 691-700 (1992); Yamamoto, K. et al. Oncogene 8, 2617-2625 (1993) | *MLL* (11q23)<br>*ENL* (19p13) | A-T hook/Zn-finger<br>Ser-Pro rich | A-T hook + Ser-Pro | pre-B-ALL/ T-ALL/ ANLL |

(57) Abstract: The invention relates generally to methods of treating cell proliferative diseases with HSP90 inhibitors and, depending on the specific aspect and embodiment(s) claimed, to the treatment of proliferative diseases that are associated with fusion proteins, e.g., bcrabl, or mutant proteins or cellular protein isoforms, e.g., mutant forms of p53.

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# Methods for Treating Genetically-Defined Proliferative Disorders with HSP90 Inhibitors

## Field of the Invention

The field of the invention relates to chemotherapeutic treatments of proliferative disorders, including rheumatoid arthritis and neoplasias.

## Background of the Invention

The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art, or relevant, to the presently claimed inventions, or that any publication specifically or implicitly referenced is prior art.

The eukaryotic heat shock protein 90s (HSP90s) are ubiquitous chaperone proteins that are involved in folding, activation and assembly of a wide range of proteins, including key proteins involved in signal transduction, cell cycle control and transcriptional regulation. HSP90 proteins are highly conserved in nature (see, e.g., NCBI accession # P07900 (SEQ ID NO: 318) and XM 004515(SEQ ID NOs: 319 and 320) (human α and β HSP90, respectively), P11499 (SEQ ID NO: 321) (mouse), AAB23369 (SEQ ID NO: 322) (rat), P46633 (SEQ ID NO: 323) (chinese hamster), JC1468 (SEQ ID NO: 324) (chicken), AAF69019 (SEQ ID NO: 325) (fleshfly), AAC21566 (SEQ ID NO: 326) (zebrafish), AAD30275 (SEQ ID NO: 327)(salmon), AAC48718 (SEQ ID NO: 328) (pig), NP 015084(SEQ ID NO: 329) (yeast), and CAC29071 (SEQ ID NO: 330) (frog).

Researchers have reported that HSP90 chaperone proteins are associated with important signaling proteins, such as steroid hormone receptors and protein kinases, including many that are implicated in tumorigenesis, *e.g.*, Raf-1, EGFR, v-Src family kinases, Cdk4, and ErbB-2 ( Buchner J., 1999, *TIBS*, 24:136-141; Stepanova, L. *et al.*, 1996, *Genes Dev.* 10:1491-502; Dai, K. *et al.*, 1996, *J. Biol. Chem.* 271:22030-4). *In vivo* and *in vitro* studies indicate that certain co-chaperones, *e.g.*, Hsp70, p60/Hop/Sti1, Hip, Bag1, HSP40/Hdj2/Hsj1, immunophilins, p23, and p50, may assist HSP90 in its function (Caplan, A., 1999, *Trends in Cell Biol.*, 9: 262-68).

Ansamycins are antibiotics derived from Streptomyces *hygroscopicus* which are known to inhibit HSP90s. These antibiotics, *e.g.*, herbimycin A (HA) and geldanamycin (GM), as well as other HSP90 inhibitors such as radicicol, bind tightly to an N-terminal pocket in HSP90 (Stebbins, C. *et al.*, 1997, *Cell*, 89:239-250). This pocket is highly conserved and has weak

homology to the ATP-binding site of DNA gyrase (Stebbins, C. *et al.*, *supra*; Grenert, J.P. *et al.*, 1997, *J. Biol. Chem.*, 272:23843-50). ATP and ADP have been shown to bind this pocket with low affinity, and HSP90 itself has been shown to have weak ATPase activity (Proromou, C. *et al.*, 1997, *Cell*, 90: 65-75; Panaretou, B. *et al.*, 1998, *EMBO J.*, 17: 4829-36). *In vitro and in vivo* studies have demonstrated that occupancy of the N-terminal pocket of HSP90 by ansamycins and other inhibitors alters HSP90 function and inhibits client protein folding. At high concentrations, ansamycins and other HSP90 inhibitors have been shown to prevent binding of client protein substrates to HSP90 (Scheibel, T., H. *et al.*, 1999, *Proc. Natl. Acad. Sci. U S A* 96:1297-302; Schulte, T. W. *et al.*, 1995, *J. Biol. Chem.* 270:24585-8; Whitesell, L., *et al.*, 1994, *Proc. Natl. Acad. Sci. U S A* 91:8324-8328). Ansamycins have also been demonstrated to inhibit the ATP-dependent release of chaperone-associated protein substrates (Schneider, C., L. *et al.*, 1996, *Proc. Natl. Acad. Sci. U S A*, 93:14536-41; Sepp-Lorenzino *et al.*, 1995, *J. Biol. Chem.* 270:16580-16587), and some of these substrates have been shown to be degraded by a ubiquitin-dependent process in the proteasome (Schneider, C., L., *supra*; Sepp-Lorenzino, L., *et al.*, 1995, *J. Biol. Chem.*, 270:16580-16587; Whitesell, L. *et al.*, 1994, *Proc. Natl. Acad. Sci. USA*, 91: 8324-8328).

This substrate destabilization occurs in tumor and nontransformed cells alike and has been shown to be especially effective on a subset of signaling regulators, *e.g.*, Raf (Schulte, T. W. *et al.*, 1997, *Biochem. Biophys. Res. Commun.* 239:655-9; Schulte, T. W., *et al.*, 1995, *J. Biol. Chem.* 270:24585-8), nuclear steroid receptors (Segnitz, B., and U. Gehring. 1997, *J. Biol. Chem.* 272:18694-18701; Smith, D. F. *et al.*, 1995, *Mol. Cell. Biol.* 15:6804-12 ), *v-src* (Whitesell, L., *et al.*, 1994, *Proc. Natl. Acad. Sci. U S A* 91:8324-8328) and certain transmembrane tyrosine kinases (Sepp-Lorenzino, L. *et al.*,. 1995, *J. Biol. Chem.* 270:16580-16587) such as EGF receptor (EGFR) and Her2/Neu (Hartmann, F., *et al.*, 1997, *Int. J. Cancer* 70:221-9; Miller, P. *et al.*, 1994, *Cancer Res.* 54:2724-2730; Mimnaugh, E. G., *et al.*, 1996, *J. Biol. Chem.* 271:22796-801; Schnur, R. *et al.*, 1995, *J. Med. Chem.* 38:3806-3812). The ansamycin-induced loss of these proteins leads to the selective disruption of certain regulatory pathways and results in growth arrest at specific phases of the cell cycle (Muise-Heimericks, R. C. *et al.*, 1998, *J. Biol. Chem.* 273:29864-72), and apoptsosis of cells so treated (Vasilevskaya, A. et al., 1999, *Cancer Res.*, 59:3935-40).

Growth arrest of this sort, provided it can be made selective, has important ramifications for the treatment of certain proliferative disorders, including cancer. Whereas cancer treatments have thus far been limited to traditional surgical removal, radiation, and/or chemotherapy, and

whereas these procedures have been more or less successful, a need remains to develop additional therapies with increased efficacy and decreased side-effects that can be used alone or in combination with existing therapies. There particularly remains a need for cancer treatments that target specific cancer types. The present invention satisfies these needs and provides related advantages as well.

## Summary of the Invention

Applicants report that many proliferative disorders are associated with aberrant proteins that exhibit a dependence on HSP90. In some cases this dependence manifests as a heightened sensitivity to HSP90 inhibitors such that affected cells can be selectively treated using a dosage that is effective against the aberrant cells but which is ineffective or less effective against normal cells. The aberrant proteins may also exhibit increased proteosome-dependent degradation when in the presence of HSP90 inhibitors. While the invention is not limited by mechanism, increased dependence, sensitivity, and /or disposition to preferential degradation may advantageously be used to treat corresponding proliferative diseases according to the methods of the invention.

Among others, the invention targets two groups of aberrant proteins in particular and the corresponding proliferative disorders they are associated with. Within the first group are fusion proteins generated as a result of non-random chromosomal aberrations (such as translocations, deletions and inversions) that juxtapose parts of the coding sequences of two normal cellular proteins (Rabbitts, T., 1994, *Nature* 372:143-149). Duplication of genetic material within a chromosome resulting in a augmented or semi-duplicative transcripts is also a possibility. Within the second group are mutants and isoforms of cellular proteins that override, dominate, or otherwise obscure the natural gene products and their function. For example, mutants and isoforms of p53 family proteins and other tumor suppressor gene products can act as dominant-negative inhibitors of the corresponding normal protein in heterozygous tumor cells (Blagosklonny, M., *et al*, 1995, *Oncogene*, 11:933-939. Other examples include virally-encoded species of certain kinases, such as v-*src* and other dominantly-acting mutant oncogene products (Uehara, Y. *et al.*, 1985, *supra*).

Accordingly, in a first aspect the invention features a method of treating a patient having a genetically-defined proliferative disease characterized by a non-random chromosomal aberration. This aberration produces or is capable of producing an oncogenic fusion protein. The method in its broadest embodiment includes (a) providing a

cell, tissue, or fluid sample of a patient suspected of having a genetically-defined proliferative disease; (b) identifying in the cell, tissue, or fluid sample one or more characteristics indicative of the proliferative disease; and (c) administering to the patient a pharmaceutically effective amount of an HSP90-inhibiting compound.

The patient may be any organism that can manifest a proliferative disease characterized by an oncogenic fusion protein, which disease is responsive to HSP90 inhibitors. Preferably, but not necessarily, the organism is an animal, more preferably a mammal, and most preferably a human.

In preferred embodiments, the inhibitory compound is an ansamycin including but not limited to, *e.g.*, geldanamycin, the geldanamycin derivative, 17-AAG, herbimycin A, and/or macbecin. Most preferably, the ansamycin is 17-AAG. These and other ansamycins and methods of preparing them are well-known in the art. *See, e.g.*, US Patents 3,595,955, 4,261,989, 5,387,584, and 5,932,566. Although preferably the compound is an ansamycin, the method may make use of any compound, synthetic or nonsynthetic, that can inhibit HSP90. Preferably, the inhibitor binds the ATP-binding site of HSP90, or an HSP90 homolog. Radicicol is a nonsynthetic example of a compound useful in the invention described and claimed herein. Libraries of small molecules, synthetic and/or nonsynthetic exist or can be made according to routine, well-known methods and screened for HSP90 binding and/or inhibitory activity. These molecules with HSP90 binding and/or inhibitory activity are also useful in the methods of the invention.

In the identifying step of the invention, which is carried out prior to diagnosis where/when there is no previous diagnosis, any technique can be used that can identify or predict a proliferative disorder targetable by HSP90 inhibitors. Especially preferred are antibody-based and nucleic acid hybridization and/or amplification techniques. Immunoprecipitation, western blotting, and immunoblotting are illustrative examples of antibody-based methods. The antibodies may be monoclonal and/or polyclonal. Illustrative examples of nucleic acid hybridization-based techniques involve Southern blotting, northern blotting, and dot-blotting. Illustrative examples of nucleic acid amplification include standard polymerase chain reactions and variations thereof, *e.g.*, reverse transcriptase-PCR (RT-PCR). The latter is especially useful for identifying levels of gene expression. Other techniques such as the ligase chain reaction (LCR) are also

well-known and have the ability to distinguish an aberrant gene (and indirectly a protein product produced therefrom) from a normal one, or at least predict genotype and/or phenotype. Other methods of identification include ligand-binding assays and gel-retardation assays that display characteristic binding affinities and/or mobility profiles for normal and variant proteins. Where the fusion protein is also an enzyme, one can establish and/or measure aberrance by enzymatic activity (or lack thereof). Conventional and derivative karyotyping and cytochemical techniques can also be used to identify a proliferative disorder of the invention prior to administration of HSP90-inhibitors. One such method is fluorescent *in situ* hybridization (FISH).

In some embodiments, the proliferative disease is a hematopoietic disorder including but not limited to one selected from the group consisting of T or B cell lymphomas, chronic myeloid leukemias (CMLs), acute promyelocytic leukemias (APLs), acute lymphoid or lymphoblastic leukemias (ALLs), acute myeloid leukemias (AMLs), non-Hodgkin lymphomas (NHLs), and chronic myelomonocytic leukemias (CMMLs). In other embodiments, the disease is characterized by a solid tumor, preferably including but not limited to papillary thyroid carcinoma, Ewing's sarcoma, melanoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma. The embodiments are not necessarily mutually exclusive of one another, and treatment of multiple distinct diseases may simultaneously be effected in a given patient, as the invention has broad-spectrum merit against a variety of different proliferative disorders.

Targeted fusion proteins may contain one or more functional domains or portions thereof, e.g., kinases, DNA binding motifs, etc. Such domains are well-known in the art. Figure 1 illustrates several types of these domains, and the specific fusion proteins, genes, and diseases they can beassociated with.

Administration may be by a variety of means. In some preferred embodiments, administration is made *ex vivo*, *e.g.*, removing and treating blood or tissue that is thereafter administered back into the patient. Alternatively, or in combination, administration may be intralesional, *e.g.*, administered to the site of a solid tumor, and/or parenteral. These constitute just some of the many different modes of administration that can be used. Others are described herein.

In other embodiments, the HSP90-inhibiting compound has an $IC_{50}$ that is higher (preferably two-fold, more preferably five-fold, and most preferably ten-fold) for cells that do not have characteristics indicative of the proliferative disorder as compared with those cells that do have such characteristics.

In other embodiments, the patient may be tested pre- and/or post-administration for sensitivity and or effect of one or more HSP90 inhibitors. This may be done *in vitro* or *in vivo*.

Numerous non-random chromosomal aberrations exist that are associated with proliferative disorders. These include but are not limited to chromosomal translocations, inversions, and deletions. Duplications also account for some aberrant chromosomes and aberrant resulting gene products. All aberrations can be targeted in various aspects of the invention. Illustrative examples of specific aberrations include those listed in Figure 1, which is adapted from Table 1 of Rabbitts, Nature 372:143-149 (1994), and others including but not limited to: inv14 (q11; q32), t(9; 22)(q34; q11), t(1; 19)(q23; p13.3), t(17; 19)(q22; p13), t(15; 17)(q21-q11-22), t(11; 17)(q23; q21.1), t(4; 11)(q21; q23), t(9; 11)(q21; q23), t(11; 19)(q23; p13), t(X; 11)(q13; q23), t(1; 11)(p32; q23), t(6; 11)(q27; q23), t(11; 17)(q23; q21), t(8; 21)(q22; q22), t(3; 21)(q26; q22), 5(16; 21)(p11; q22), t(6; 9)(p23; q34), 9; 9?, t(4; 16)(q26; p13), inv(2; 2)(p13; p11.2-14), inv(16)(p13q22), t(5; 12)(q33; p13), t(2; 5)(2p23; q35), t(9:12)(q34:p13), del(12p), t(9;22),+8,+Ph,i(17q), t(15;17)(q22;q12), t(11;17)(q23;q12), t(16:16)(p13;q22), inv(16)(p13;q22), t(9;11)(p22;q23), t(1;22)(p13;q13), t(3;3)(q21;q26), inv(3)(q21q26), t(3;5)(q21;q31), t(3;5)(q25;q34), t(7;11)(p15;p15), t(8;16)(p11;p13), t(9;12)(q34;p13), t(12;22)(p13;q13), del(5q), del(7q), del(20q), t(11q23), t(12;21)(p13;q22), t(5;12)(q31;p13), t(1;12)(q25;p13), t(12;15)(p13;q25), t(1;12)(q21;p13), t(12;21)(q13;p32), and t(5;7)(q33;q11.2). These are merely a sampling of the many chromosomal aberrations well-known in the art that give rise to particular proliferative disorders treatable according to the invention. For these and others, *see, e.g.*, the National Center for Biotechnology Information (NCBI) databases, including, e.g., the Online Mendelian Inheritance in Man (OMIM) database and related links to nucleotide and protein sequences. For purposes of the present invention, the underlying genetic sequences affected are for the most part known and/or may be deduced using techniques routine in the art.

Targeted in particularly preferred embodiments of the invention are chromosomal aberrations corresponding to t(9; 22)(q34; q11) that give rise to bcr-abl fusion proteins, chronic myelogenous leukemia (CML) and, in some cases, acute lymphoid or lymphoblastic leukemia (for ALL, *see, e.g.*, Erikson et al., *Heterogeneity of chromosome 22 breakpoint in Philadelphia-positive (Ph+) acute lymphocytic leukemia*, Proc. Nat. Acad. Sci. 83: 1807-1811 (1986))).

In a second aspect, the invention features a method of treating cancerous cells in a heterogeneous population of cells. The heterogeneous population includes both cancerous and noncancerous cells, and the cancerous cells are further characterized by fusion proteins that are not produced in the noncancerous cells. The method includes administering to the heterogeneous population a pharmaceutically effective amount of an HSP90-inhibiting compound. The population may be tested by separation of samples from each population into separate subpopulations, cancerous or noncancerous, *e.g.*, where cultured cells of each are tested in parallel for response and/or susceptibility to an HSP90-inhibitor or candidate inhibitor molecule. Alternatively, the population may be mixed, *e.g.*, in an *ex vivo* procedure in which cells of a patient, *e.g.*, blood, are treated and administered back to the patient or to another individual. This method otherwise tracks the various described and/or claimed embodiments and/or combinations of embodiments of the first aspect.

In a third aspect, the invention features a method of treating a patient having a proliferative disease associated with a mutant protein or cellular protein isoform dependent on HSP90, or which disease is otherwise sensitive to HSP90 inhibitors. The method includes (a) providing a cell, tissue, or fluid sample of a patient suspected of having said proliferative disease; (b) identifying in the cell, tissue, or fluid sample one or more characteristics indicative of a mutant or cellular protein isoform; and (c) administering to the patient a pharmaceutically effective amount of an HSP90-inhibiting compound.

In preferred embodiments, the mutant protein or cellular protein isoform is selected from the group consisting of src, RET, p53, p51, p63, and p73. Most preferably selected are isoforms of p53 selected from N239S, C176R, and R213*, Y236delta, C174Y, M133T, G245D, E258K, 1-293delta, G245C, R248W, E258K, R282W, R175H, R280K,

V143A, R175H, P177S, H178P, H179R, R181P, 238-9delta, G245S, G245D, M246R, R248Q, R249S, R273H, R273C, R273L, and D281Y.

In another preferred embodiment, the proliferative disease to be treated is rheumatoid arthritis.

In some embodiments, the mutant protein or cellular protein isoform may give rise to a dominant negative phenotype In other embodiments, the mutant or cellular protein isoform may give rise to a dominant positive mutant. In either embodiment, the patient may be heterozygous for the normal cellular gene. Other embodiments track those listed for the preceding aspects.

In a fourth aspect, the invention features a method of selectively treating cells that express a mutant protein or cellular protein isoform associated with a proliferative disorder and which mutant/isoform is dependent on HSP90, or which disease is otherwise sensitive to HSP90 inhibitors. The method includes (a) providing a population of cells in which at least some of the population express a mutant protein or cellular protein isoform that is dependent on HSP90 or which are otherwise sensitive to HSP90 inhibitors. The method further includes administering to the population a pharmaceutically effective amount of an HSP90-inhibiting compound. The embodiments for this aspect may otherwise track preceding embodiments.

The foregoing aspects contemplate treatment of existing cell proliferative disorders. It is expected that the invention may also find use in prophylactic prevention of various proliferative disorders of the invention. Further, and where appropriate, each of the embodiments discussed above and different combinations thereof, including subgenus and sub-Markush groups, may cross-apply to each of the different aspects of the invention. Further, where sequence listings are provided, the invention may in some aspects contemplate subsequences of the primary sequence listings. Any subsequence within such primary listing is also contemplated for the invention, as well as all allelic variants, and mutant variants and isoforms thereof, as well as corresponding homologs from other organisms and species. Sequences contiguous with and/or in addition to the listed sequences and their above equivalents are also contemplated.

Advantages of the invention include broad-acting treatment or prophylaxis directed to a variety of different proliferative disorders. Other advantages include the efficient and rapid diagnosis and care of patients suffering from proliferative disorders, with minimal apparent adverse effects. Still other advantages, aspects, and embodiments will be apparent from the figures, the detailed description, and the claims.

## Brief Description of the Drawings

Figure 1 illustrates various genetically defined diseases characterized by non-random chromosomal aberrations that give rise to oncogenic fusion proteins. These illustrative aberrations, diseases, and fusion proteins are targeted in various embodiments of the invention. Other targeted aberrations, diseases, and fusion proteins may be found in the specification and in sources commonly known in the art, e.g., the NCBI and GenBank databases, and journal literature.

## Detailed Description of the Invention

### *Definitions*

As used herein and in the claims the following terms have the following meanings:

A "genetically-defined disease" is one with a basis in DNA. Genetically defined diseases of the invention include "cell proliferative disorders" wherein unwanted cell proliferation of one or more subset(s) of cells in a multicellular organism occurs, resulting in harm, for example, pain or decreased life expectancy to the organism. "Cell proliferative disorders" refer to disorders wherein unwanted cell proliferation of one or more subset(s) of cells in a multicellular organism occurs, resulting in harm, for example, pain or decreased life expectancy to the organism. Cell proliferative disorders include, but are not limited to, cancers, tumors, benign tumors, blood vessel proliferative disorders, autoimmune disorders and fibrotic disorders. These disorders are not necessarily independent. For example, fibrotic disorders may be related to, or overlap with, blood vessel disorders, *e.g.*, atherosclerosis (which is characterized herein as a blood vessel disorder that is associated with the abnormal formation of fibrous tissue).

A "non-random chromosomal aberration" is one that occurs with a nonrandom frequency or is selected for in a population of individuals. Chromosomal aberrations of the invention include translocations, *i.e.*, relocation of a fragment of one chromosome onto another

chromosome; inversions, *i.e.*, wherein pieces of a chromosome rotate within the same chromosome, and deletions, *i.e.*, wherein fragments of a chromosome are lost thereby juxtaposing pieces of DNA that previously did not reside immediately beside each other.

An "oncogenic fusion protein" is a protein that is non-natural in and of itself but that may contain one or more pieces of other proteins that may or may not naturally occur within a cell. The fusion protein functions by improperly stimulating cell growth, directly or indirectly. In the context of the invention, the term is also associated with a cellular proliferative disease and is preferably encoded by a nucleic acid found in the cell, *e.g.*, as part of a non-random chromosomal aberration. An oncogenic fusion protein may contain domains or portions thereof, *e.g.*, kinases and/or DNA binding proteins that are well known in the art, or else predicted from their structure to behave as such.

A "fusion" may relate to, as appropriate to a given context, a fusion chromosome, an abnormal mRNA transcribed from the fused portion of the chromosome, or a polypeptide product translated from the abnormal mRNA that is transcibed from the fusion chromosome. These fusions may result from chromosomal deletions, insertions, and/or translocations. Domains or portions of different genes and gene products are frequently, although not necessarily always, brought together as a consequence of the fusion event. For example, an intragenic deletion can result in an intragenic fusion and give rise to an abnormal protein lacking a component from a second gene. More frequently it occurs that two genes or portions thereof are juxtaposed more or less, transcribed together as a single transcript, and translated together as a fusion protein bearing contributions from multiple genes or other chromomosal DNA pieces. In such fusions, reading frames can be preserved, e.g., as in preserved functional domains or portions thereof coming from two or more different genes, or else the reading frame can be disrupted, e.g., as in the case of a "missense" or "nonsense" event as these terms are known in the art.

By "providing a cell, tissue, or fluid sample of a patient suspected of having said genetically-defined disease" and "identifying one or more characteristics indicative of said disease in or on said cell, tissue, or fluid sample" can mean, although is not limited to the situation where, the sample is withdrawn from the patient in order to perform the analysis or analyses. Many invasive and noninvasive procedures exist, e.g., NMR, ultrasound and other imaging techniques, that can be used to diagnose, at least in part, an illness and its cause. For example, "tagged" antibodies or other ligands with affinity for a fusion protein or chromosomal aberrancy or

aberrancy product of the invention can be used to make the diagnosis and/or assist in treatment according to methods of the invention.

"Characteristics indicative of said disease" may embrace phenotypes or genotypes and may be measured qualitatively or quantitatively by a variety of techniques. The characteristics may be observed with the naked eye or else through the assistance of a machine or other diagnostic technique(s). Exemplary techniques of measurement include but are not limited to immunoreactivity and/or precipitation, PCR, LCR, karyotyping, and fluorescence activated cell sorting ("FACS)" as those terms are known and understood in the art.

"Administering" can be by direct means, *e.g.,* intralesional or by parenteral or peripheral administration to a patient, or else by indirect means, *e.g.*, as by withdrawing a patient's cells, treating them, and then re-introducing them back into the patient. The latter constitutes an "*ex vivo*" technique.

An "HSP90-inhibiting compound" is one that disrupts the expression, structure, and/or function of an HSP90 chaperone protein and/or a protein that is dependent on HSP90. HSP90 proteins are highly conserved in nature (see, *e.g.*, NCBI accession #'s P07900 and XM 004515 (human α and β HSP90, respectively), P11499 (mouse), AAB2369 (rat), P46633 (chinese hamster), JC1468 (chicken), AAF69019 (flesh fly), AAC21566 (zebrafish), AAD30275 (salmon), O02075 (pig), NP 015084 (yeast), and CAC29071 (frog). There are thus many different HSP90s, all with anticipated similar effect and similar inhibition capabilities. The HSP90 inhibitor used in the methods of the invention may be specifically directed against an HSP90 of the specific host patient or may be identified based on reactivity against an HSP90 homolog from a different species, or an artificial HSP90 variant. The inhibitors used may be ring-structured antibiotics, *e.g.*, benzoquinone ansamycins, or other types of molecules, *e.g.*, antisense nucleic acids and molecules such as radicicol.

An "ansamycin" includes but is not limited to geldanamycin, 17-AAG, herbimycin A, and macbecin. The specific ansamycin 17-AAG stands for 17-allylamino-17-demethoxygeldanamycin. This and other ansamycins that can be used are well-known in the art. *See, e.g.*, U.S. Patent Nos. 3,595,955, 4, 261, 989, 5,387,584, and 5,932,566. Ansamycins may be synthetic, naturally-occurring, or else derivatives of naturally occurring ansamycins that are prepared using standard chemical derivatization techniques.

A "pharmaceutically effective amount" means an amount which is capable of providing a therapeutic or prophylactic effect. The specific dose of compound administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the specific compound administered, the route of administration, the condition being treated, the individual being treated, and the tissue or cell type targeted (or not targeted). A typical daily dose (administered in single or divided doses) will contain a dosage level of from about 0.01 mg/kg to about 100 and more preferaby 50 mg/kg of body weight of an active compound of this invention. Preferred daily doses generally will be from about 0.05 mg/kg to about 20 mg/kg and ideally from about 0.1 mg/kg to about 10 mg/kg.

A preferred therapeutic effect is the inhibition to some extent of the growth of cells causing or contributing to a cell proliferative disorder. A therapeutic effect will also normally, but need not, relieve to some extent one or more of the symptoms of a cell proliferative disorder other than cell growth or size of cell mass. In reference to the treatment of a cancer, a therapeutic effect refers to one or more of the following: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (*i.e.*, slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 3) inhibition (*i.e.*, slowing to some extent, preferably stopping) of tumor metastasis; 4) inhibition, to some extent, of tumor growth; and/or 5) relieving to some extent one or more of the symptoms associated with the disorder.

In reference to the treatment of a cell proliferative disorder other than a cancer, a therapeutic effect refers to either: 1) the inhibition, to some extent, of the growth of cells causing the disorder; 2) the inhibition, to some extent, of the production of factors (*e.g.*, growth factors) causing the disorder; and/or 3) relieving to some extent one or more of the symptoms associated with the disorder.

With respect to viral infections, the preferred therapeutic effect is the inhibition of a viral infection. More preferably, the therapeutic effect is the destruction of cells which contain the virus.

A "cancer" refers to one or more various types of benign or malignant neoplasms. In the case of the latter, these may invade surrounding tissues and may metastasize to different sites, as defined in Stedman's Medical Dictionary 25th edition (Hensyl ed. 1990).

The term "$IC_{50}$" is defined as the concentration of an HSP90 inhibitor required to achieve killing or other growth inhibition of 50% of the cells of a homogenous cell type population, or of a particular cell type, *e.g.*, cancerous versus noncancerous, over a period of time. The $IC_{50}$ is preferably, although not necessarily, greater for normal cells than for cells exhibiting a proliferative disorder.

The term "mutant or isoform cellular protein" refers to a variation of a wild-type protein that occurs in a cell and has a particular function. The mutant or isoform cellular protein of the invention preferably associates with or gives rise to a proliferative disorder, *e.g.*, a cancer, whereas the wild-type protein ordinarily does not.

**General**

As described and claimed herein, ansamycins and other HSP90 inhibitors can be used to treat two important classes of tumor-promoting (oncogenic) human proteins.

**1. Oncogenic Fusion Proteins**

The first class of target proteins of the invention are fusion proteins generated as a result of non-random chromosomal aberrations (such as translocations, deletions and inversions) that juxtapose parts of the coding sequences of two normal cellular proteins (Rabbitts, T., 1994, *Nature* 372:143-149) leading to the lineage-specific expression of a mutant fusion protein that has biological activities derived from both parent proteins (Barr, F, 1998, *Nat. Genet.* 19:121-124). Without being limiting of the invention, Applicants have discovered that these fusion proteins have a heightened dependence on HSP90 chaperone activity, and/or decreased stability in the presence of HSP90 inhibitors, thus making them selective targets for treatment with HSP90 inhibitors.

**a. Bcr-abl as an example**

One example of heightened HSP90 dependence and inhibitor sensitivity is observed when chronic myelogenous leukemia (CML) cells harboring the fusion oncoprotein p210-bcr-abl are treated with HSP90 inhibitors. This fusion protein is degraded faster and more completely than wild type c-abl protein (An, W *et al*, 2000, *Cell Growth and Differentiation* 11: 355-360). Further experimental evidence that bcr-abl expressing leukemia cells are more sensitive to HSP90 inhibitors than are closely related bcr-abl-negative leukemia lines is found in Honma, Y *et al*,

1995, *Int. J. Cancer* 60:685-688, where it is reported that the $IC_{50}$ of herbimycin A in six bcr-abl expressing leukemia cell lines averaged 29.3 nM as compared to a mean $IC_{50}$ of 399.3 nM in a panel of four bcr-abl-negative leukemia lines. Illustrative protein and nucleic acid sequences corresponding to embodiments of bcr-abl fusions of the invention include but are not limited to those found in SEQ ID NOs 1-26 and subsequences thereof, which are further discussed below, along with corresponding NCBI accession numbers.

The normal Bcr gene occupies a region of about 135 kb on chromosome 22. It is expressed as mRNAs of 4.5- and 6.7-kb, which apparently encode for the same cytoplasmic 160-kD protein, and contains 23 exons as well as an unusual inverted repeat flanking the first exon. The BCR protein reportedly contains a unique serine/threonine kinase activity and at least two SH2 binding sites encoded in its first exon and a C-terminal domain that functions as a GTPase activating protein for p21(rac) (Diekmann et al., Nature 351: 400-402 (1991). Chissoe et al., Genomics 27: 67-82 (1995), sequenced the complete BCR gene and greater than 80% of the human ABL gene, which are both involved in the t(9;22) translocation (Philadelphia chromosome) associated with more than 90% of chronic myelogenous leukemia, 25 to 30% of adult and 2 to 10% of childhood acute lymphoblastic leukemia, and rare cases of acute myelogenous leukemia. Comparison of the gene with its cDNA sequence revealed the positions of 23 BCR exons and putative alternative BCR first and second exons. From the sequence of four newly studied Philadelphia chromosome translocations and a review of several other previously sequenced breakpoints, Chissoe et al. found a variety of breakpoints and recombinations sites possible within the genes. Thus, despite the normal chromosomes and genes each being known (9 and 12; bcr and abl), and the fact that combinations of these genes are known to lead to forms of CML and ALL, the precise genetic breakpoint/recombination junctions that lead to these diseases can vary.

This heterogeneity likely also applies to some non bcr-abl chromosomal aberrations of the invention as well. Nevertheless, because the genes and/or chromosomes involved are known to have a part in the disorders, the disorders are said to be "genetically defined."

**b. Other oncogenic fusion proteins**

Oncogenic fusion proteins in general are thought to be inherently unstable. To the extent these unstable oncogenic fusion proteins make use of HSP90, they are susceptible of the methods claimed herein. Because the fusion genes and their protein products exert overtly oncogenic activity (Deininger, M *et al*, 2000, *Cancer Res.* 60:2049-2055), preferential degradation of these labile proteins induced by HSP90 inhibitors will have therapeutic value in diseases where the fusion protein is expressed. The present invention thus includes treatment of patients with tumors that are dependent upon other oncogenic fusion proteins that arise from non-random genetic aberrations. An illustrative but nonexhaustive list of these tumors is included in Figure 1, adapted from Table 1 of Rabbitts, T., 1994, *Nature* 372:143-149. The list may be supplemented by additional information found, *e.g.*, in Rowley, J, 1999, *Semin. Hematol.* 36:59-72 and other publications known in the art, as well as discussion below.

Myeloid cancers in particular are within the scope of the invention and include chromosomal abnormalities that give rise to oncogenic fusion proteins that drive the growth of chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), and acute lymphoblastic leukemia (ALL). The following chromosomal aberrancies give rise to some illustrative fusions implicated in various forms of ALL:

t(1:19)(q23:p13) Pro-pre-B acute lymphoblastic leukemia

t(12:21)(p13:q32) Pro-pre-B acute lymphoblastic leukemia

t(9:22)(q34:q11) B or B-myeloid acute lymphoblastic leukemia

t(9:12)(q34:p13) Acute B-lymphoblastic leukemia

del(12p) Acute B-lymphoblastic leukemia

Specific genes and proteins thereof implicated in various ALL forms include the *MLL* gene and the *TEL* gene, which are commonly rearranged in tumors. Rowley, J, *supra*. Each has numerous fusion partners. ETV6 denotes the name of the TEL gene product. Fusion of TEL/ETV6 to an acyl CoA synthetase, ACS2, results from a t(5;12)(q31;p13) AML event(Yagasaki, F *et al*, 1999, *Genes Chromosomes Cancer* 26:192-202); fusion of TEL/ETV6 to ABL-related gene (ARG)

results from a t(1;12)(q25;p13) AML event (Iijima, Y *et al*, 2000, *Blood* 95:2126-2131); fusion of TEL/ETV6 to the neurotrophin-3 receptor TRKC results from a t(12;15)(p13;q25) AML event and gives rise to congenital fibrosarcoma (Liu, Q *et al*, 2000, *EMBO J.* 19:1827-1838, Eguchi, M *et al*, 1999, *Blood* 93:1355-1363); fusion of TEL/ETV6 to the aryl hydrocarbon receptor ARNT results from a t(1;12)(q21;p13) event and gives rise to acute myeloblastic leukemia (AML-M2) (Salomon-Nguyen, F *et al*, 2000, *Proc. Natl. Acad. Sci.* 97:6757-6762); and fusion of TEL/ETV6 toAML-1, the DNA-binding subunit of the AML-1/CBFb transcription factor results from a (12;21)(q13;p32) event that can give rise to acute lymphoblastic leukemia (ALL, Shurtleff, SA *et al*, 1995, *Leukemia* 9:1985-1989) and, in some cases, non-Hodgkin's lymphoma (NHL).

Another illutrative fusion within the scope of the invention is the EWS/FLI-1 hybrid protein that is the hallmark of Ewing's sarcoma and the primitive neuroectodermal tumor family (Silvany, *et al*, 2000, *Oncogene* 19:4523-4530).

Yet another illustrative family of fusion proteins within the scope of the invention is the group of fusion proteins arising from chromosomal rearrangements involving the *RET* gene in thyroid cancer (Kolibaba, K, *et al*, 1997, *Biochem. Biophys. Acta* 1333:F217-F248). Rearrangements of *RET*, resulting in juxtaposition of the RET tyrosine kinase domain with one of three 5' sequences (RET-PTC-1, -2 and -3) generate fusion proteins comprising the kinase domain of RET fused to parts of the genes *H4* (RET-PTC-1), *R1a* of cAMP-dependent protein kinase A (RET-PTC-2) and ELE-1 (RET-PTC-3).

The scope of the present invention also includes cancers and other proliferative diseases, e.g., rheumatoid arthritus, now known or discovered in the future to be characterized by specific chromosomal aberrations giving rise to fusion proteins.

In at least some cases, heterogeneity of breakpoints within the affected chromosomes is possible, thus providing for the possibility of many different DNA fusions and amino acid sequence variations than those specifically listed in the SEQ ID NOs provided, and which can also be formed by the chromosomal rearrangements,e.g., translocations, inversions, deletions, insertion/duplications, etc., so designated. For example, many different abl-bcr gene combinations and corresponding fusion proteins can be designated by the t(9; 22)(q34; q11) tranlocation event, and all—not just those listed below—are included within the purview of the designation, t(9;22)(q34;q11).

Aberrant proteins of the invention, at least in some instances, feature one or more properties of the individual normal parent genes' gene products (normal polypeptide gene product(s), including e.g., functional and structural domains and subportions thereof resulting from transcription and translation of normal parent genes on normal chromosomes) but otherwise lack exact identity and function with the parent genes' protein products. Chromosomal aberrations may give rise to in-frame fusions or frame-shifts, the latter of which can account for missense or nonsense translation of at least a portion of the mRNA, and thereby result in aberrant polypeptide product(s).

Of the SEQ ID NOs discussed herein, some reflect fusion genes, some reflect fusion gene products, e.g., mRNAs and peptides, and some reflect portions of such entities. Still some others reflect recombination "hot spots" in the normal genes that have a general propensity to form a chromosomal aberration. Each of the above sequences may be useful as diagnostic markers in appropriate embodiments of the invention and/or may be characteristic of a given proliferative disorder (or patient exhibiting such and, accordingly, a candidate for treatment according to some methods of the invention.

While the specific sequences discussed are predominantly human in origin, it is understood that other animal "homologs" of the corresponding human sequences are known in the art and are intended to be within within the purview of various aspects of the invention. Because HSP90s are also found in plants, plants and plant cells and tissues exhibiting fusion protein products that give rise to undesirable traits may also be treatable in some aspects and embodiments of the invention. The NCBI nucleotide and protein databases are an example of where such sequences can be found. It is also appreciated that the complete human genome and other genomes have been sequenced, and continue to be sequenced at a hight rate, thus facilitating the identity of sequences contiguous with those listed herein and homologs thereto.

Further, some of the sequences listed herein may contain errors associated with the logistical complexities of compiling such extensive data, and the true sequences should be interpreted to be within the scope of the invention, either literally or under the doctrine of equivalents, as they are known in the art.

As those of ordinary skill will appreciate, allelic variations and different isotype proteins are also possible for some genes, e.g., the product of differential splicing events in

mRNA, and these are likewise considered within the scope of the invention. Further, some of the NCBI and SEQ ID NOs listed below are for wild-type genes, and are included to give an indication of the different chimeric possibilities for the fused counterpart during a chromosomal aberration according to the invention. Should any of the sequences listed below be in error, such should be construed consistent with what is commonly understood in the art—irrespective of how presented in the application.

### c. Further Discussion of Illustrative Chromosomal Aberrancies

*Convention: where two or more SEQ ID NOs are provided per NCBI accession #, peptide(s) shall be listed first where applicable, followed by corresponding mRNA/cDNA and/or genomic sequence as the case may be. The terms "nucleotide" and "nucleotides" are interchangeable with, and may be symbolized by, "nt."*

**t(9; 22)(q34; q11)**

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S72478, corresponding to SEQ ID NOs 1 and 2, illustrates one aberrant polypeptide/mRNA in a patient having CML and another patient having ALL. The junction for the nucleic acid sequence between the BCR and ABL genes is stated to reside between nucleotides 100 and 101., with 1-100 derived from BCR and 101-140 derived from ABL.

NCBI #M19695 (SEQ ID NO 3) illustrates a nucleic acid sequence identified from a human myelocytic chimeric bcr/chromosome 9 fusion (CML K562 cell line).

NCBI #M30829 (SEQ ID NOs 4 and 5) illustrates a partial bcr/abl fusion protein mRNA.

NCBI #M13096 (SEQ ID NO 6) illustrates a human chimeric bcr/c-abl fusion protein gene characteristic of cell line K562.

NCBI #M30832 (SEQ ID NOs 7 and 8) corresponds to a human bcr/abl fusion protein, partial cds, clone E3 from cell line EM2.

NCBI # AJ131466 (SEQ ID NOs 9 and 10) corresponds to a partial human bcr/abl (major breakpoint) fusion peptide and the underlying nucleic acid encoding it. Nucleotides 1-373 are said to derive from exons 11-14 of the bcr gene, and nucleotides 374-997 are said to derive from exons 2-4 of the abl gene.

NCBI # AF192533 (SEQ ID NOs 11 and 12) corresponds to a partial human bcr/abl (major breakpoint) fusion mRNA. Nucleotides 1-289 are said to come from the bcr gene of chromosome 22 and nucleotides 290-305 from the able gene of chromosome 9.

NCBI # AF321981 (SEQ ID NO 13) corresponds to a BCR-ABL fusion transcript e15a2 mRNA sequence. This particular fusion is stated to result from results from a translocation between the 3' portion of the c-ABL oncogene on chromosome 9 and exon 15 of the BCR gene on chromosom22; t(9;22).

NCBI # M17543 (SEQ ID NO 14) corresponds to at least a portion of a Philadelphia chromosome breakpoint cluster region associated with one embodiment of a bcr abl fusion gene. Nucleotides 1-31 are said to be exon 1 and nucleotides 32-63 are said to be intron A.

NCBI # M17542 (SEQ ID NOs 15 and 16) corresponds to a human bcr/abl fusion protein mRNA (product of translocation t(22q11; 9q34)), exons 1 and 2. Nucleotides 1-31 are stated to denote exon 1 and nucleotides 32-63 are stated to denote exon 2.

NCBI # M17541(SEQ ID NOs 17 and 18) corresponds to a human bcr/abl fusion protein mRNA (product of translocation t(22q11; 9q34)), exons 1 and 2. Nucleotides 1-31 are stated to denote exon 1 and nucleotides 32-63 are stated to denote exon 2.

NCBI # AB069693 (SEQ ID NOs 19 and 20) denotes a human partial mRNA corresponding to a bcr/abl e8a2 fusion protein. BCR exons 7 (nucleotides 1-53) and 8 (nucleotides 54-194) are joined to ABL intron1b inverted (nucleotides 195-249) and ABL exon a2 (nucleotides 250-423).

NCBI # AJ131467(SEQ ID NOs 21 and 22) correspond to a human partial BCR/ABL chimeric fusion peptide and corresponding mRNA. Nucleotides 1-117 denote exon 1 of the bcr gene, nucleotides 118-193 and 194-298 denote exons 12 and 13 of the

bcr gene, and nucleotides 299-472, 473-768, and 769-922 respectively denote exons 2-4 of the abl gene.

NCBI # AF113911 (SEQ ID NOs 23 and 24) correspond to a partial BCR-ABL minor breakpoint peptide (BCR-ABL fusion) mRNA. Nucleotides 1-455 are stated to be from chromosome 22 and nucleotides 456-1079 from chromosome 9.

NCBI # AF251769 (SEQ ID NOs 25 and 26) correspond to a human partial bcr/abl e1-a3 chimeric fusion protein (BCR/ABLe1-a3) mRNA. Nucleotides 1-455 are stated to be from chromosome 22 and nucleotides 456-1079 from chromosome 9.

**inv14 (q11; q32)**

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # X82240 (SEQ ID NOs 27 and 28) correspond to at least a portion of an mRNA for the gene TCL1, which is disrupted in aberrations of the type noted.

NCBI # NM_021966 (SEQ ID NOs 29 and 30) relate to a human T-cell leukemia/lymphoma 1A (TCL1A), mRNA.

NCBI # X82241 (SEQ ID NO 31) relates to a 5' portion of a human TCL1 gene. Nucleotides 496-560 are said to correspond to exon 1.

NCBI # M14198 (SEQ ID NOs 32 and 33) relate to a human chromosome 14 paracentric inversion producing an heavy chain/T-cell receptor J-alpha fusion protein.

NCBI # X03752 (SEQ ID NOs 34 and 35) relate to a human gene for rearranged Ig V(H) are said to encode the IgVH region (108 aa) and nucleotides 324 to 377 are said to encode 18 amino acids of the TCR-J-alpha protein.

NCBI # M12071 (SEQ ID NOs 36 and 37) relates to a human Ig heavy-chain V-region gene (VII family) rearranged to T-cell receptor alpha-chain D-J-sp region (IgT) in an inv(14)(q11; q32), SUP-T1 cell line. Nucleotides 121-166 are said to derive from exon 1 of the IgH gene, nucleotides 167-248 from intron 1 of the IgH gene, nucleotides 249-623 from exon 2 of the IgH gene, and nucleotides 624-675 from intron 2 of the IgH gene.

NCBI # S45947 (SEQ ID NOs 38 and 39) relate to an IgT=T cell specific exon ET-immunoglobulin VH-T cell receptor J alpha fusion [human, T cell lymphoma cell line SUP-T1, mRNA Mutant, 508 nt]. Nucleotides 34-507 are stated to be IgT coding sequence.

NCBI # S45207 (SEQ ID NOs 40 and 41) relate to an IgT=T cell specific exon ET-exon EX-immunoglobulin VH-T cell receptor J alpha fusion [human, T cell lymphoma cell line SUP-T1, mRNA Mutant, 616 nt]. Nucleotides 130-616 are stated to be IgT coding sequence.

**t(1; 19)(q23; p13.3)**

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # M31522 (SEQ ID NOs 42 and 43) relate to a human translocation (t1;19) fusion protein (E2A/PRL) mRNA, 3' end. ]. Nucleotides 1-1653 are stated to encode a portion of an E2A/PRL fusion protein.

**t(17; 19)(q22; p13)**

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # M95586 (SEQ ID NOs 44 and 45) relate to a human E2A/HLA fusion protein (E2A/HLF) mRNA, complete cds. Nucleotides 31-1755 are said to be coding sequence.

**t(15; 17)(q21-q11-22)**

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # S50916 (SEQ ID NOs 46 and 47) relate to a PML-RAR fusion gene {fusion transcript} [human, mRNA Partial, 1284 nt]. . Nucleotides 1-1251 are said to be coding sequence.

NCBI # M73779 (SEQ ID NOs 48 and 49) relate to a human PML-RAR protein (PML-RAR) mRNA, complete cds; coding sequence: nucleotides 67-2460.

NCBI # AJ417079 (SEQ ID NOs 50 and 51) relate to a human partial mRNA for PML/RARA fusion protein (PML/RARA gene); Nucleotides 1-109 derive from exon 6 of PML, nucleotides 110-172 from intron 2 of RARA, and nucleotides 173-296 from exon 3 of RARA.

**t(11; 17)(q23; q21.1)**

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # AAB29813 (SEQ ID NO 52) relates to a retinoic acid receptor alpha, RAR alpha(PLZF=zinc finger protein, PLZF-RAR alpha isoform A=fusion protein) {translocation} [human, acute promyelocytic leukemia patient, Peptide Mutant, 858 aa].

NCBI # AAB29814 (SEQ ID NO 53) relates to a PLZF=zinc finger protein(retinoic acid receptor alpha, RAR alpha, RAR alpha 1-PLZF isoform B=fusion protein) {translocation} [human, acute promyelocytic leukemia patient, Peptide Mutant, 277 aa].

**t(4; 11)(q21; q23)**

This translocation is generally addressed in Figure 1. Illustrative embodiments include but are not limited to events comprising the sequences:

NCBI # L22179 (SEQ ID NOs 54 and 55) relate to a human MLL-AF4 der(11) fusion protein mRNA, complete cds. Nucleotides 5-6940 are said to be coding sequence.

NCBI # S67825 (SEQ ID NOos 56 and 57) relate to a human ALL1-AF4 fusion protein mRNA, partial cds. Nucleotides 1-585 are said to derive from chromosome 11 and nucleotides 586-832 from chromosome 4.

NCBI # AF024541 (SEQ ID NOs 58 and 59) relate to a human MLL-AF4 fusion protein mRNA, partial cds. The codons are said to start with nucleotide 3.

NCBI # AF031404 (SEQ ID NOs 60 and 61) relate to a human MLL-AF4 fusion protein mRNA, partial cds. Nucleotides 1-305 are said to derive from chromosome 11 and nucleotides 306-741 from chromosome 4. Codons begin with nucleotide 3.

NCBI # L04731 (SEQ ID NO 63) relates to a human translocation T(4:11) of the human ALL-1 gene to chromosome 4.

NCBI # AF177237 (SEQ ID NOs 64 and 65) relate to human cell-line MV4-11, MLL/AF4 fusion protein (MLL/AF4) mRNA, partial cds. Nucleotides 1-62 derive from exon 6 of the MLL gene on chromosome 11, and nucleotides 63-450 from exon 5 of the AF4 gene on chromosome 4.

NCBI # AF177236 (SEQ ID NOs 66 and 67) relate to a human A1 MLL/AF4 fusion protein (MLL/AF4) mRNA, partial cds. Nucleotides 1-63 are stated to derive from exon 6 of the MLL gene on chromosome 11, and nucleotides 64-450 from exon 5 of the AF4 gene on chromosome 4.

NCBI # AF031403 (SEQ ID NO 68) relates to a human MLL/AF4 translocation breakpoint t(4;11)(q21;23). Nucleotides 1-105 are said to derive from exon 5 of MLL, nucleotides 435-508 from exon 6 of MLL, nucleotides 2195-2326 from exon 7 of MLL, nucleotides 2874-2987 from exon 8 of MLL, and nucleotides 3645-6983 from AF4.

NCBI # AF177238 (SEQ ID NOs 69 and 70) relate to a human A1 AF4-MLL fusion protein (AF4-MLL) mRNA, partial cds. Nucleotides 1-484 are said to derive from exon 3 of AF4 and nucleotides 485-596 from exon 7 of MLL.

NCBI # AF177239 (SEQ ID NOs 71 and 72) relate to a human cell-line MV4-11 AF4-MLL fusion protein (AF4-MLL) mRNA, partial cds. Nucleotides 1-484 are said to derive from exon 3 of AF4 and nucleotides 485-596 from exon 7 of MLL

NCBI # AF397907 (SEQ ID NO 73) relates to a human AF4/MLL translocation breakpoint region. Nucleotides 1-437 are said to derive from intron 3 of AF6, nucleotides 440-631 from intron 6 of MLL, and nucleotides 632-747 from exon 7 of MLL. The breakpoint is approximately nucleotide 438-439, which was undetermined due to GC compressions.

# FIGURE 1

| Type of Aberration | Background Literature | Affected Gene(s) | Protein Domain | Fusion Protein | Disease |
|---|---|---|---|---|---|
| t(9; 22)(q34; q11) | de Klein, A. et al. Nature 300, 765-767 (1982) | *CABL* (9q34)<br>*BCR* (22q11) | tyrosine kinase<br>serine kinase | serine + tyrosine kinase | CML/ALL |
| inv14 (q11; q32) | Baer, R., Chen, K.-C., Smith, S. D. & Rabbitts, T. H. Cell 43, 705-713 (1985); Denny, C. T. et al. Nature 320, 549-551 (1986) | TCR-α (14q11)<br>VH-(14q32) | TCR-Cα<br>Ig VH | VH-TCR-Cα | T/B-cell lymphoma |
| t(1; 19)(q23; p13.3) | Kamps, M. P., Murre., C., Sun, X.-H. & Baltimore, D. Cell 60, 547-555 (1990); Nourse, J. et al. Cell 60, 535-545 (1990) | *PBX1* (1q23)<br>*E2A* (19p13.3) | HD<br>AD-b-HLH | AD + HD | pre-B-ALL |
| t(17; 19)(q22; p13) | Hunger, S. P., Ohyashiki, K. Toyama, K. & Clearly, M. L. Genes Dev. 6, 1608-1620 (1992); Inaba, T. et al. Science 257, 531-534 (1992) | *HLF* (17q22)<br>*E2A* (19p13) | bZIP<br>AD-b-HLH | AD + bZIP | pro-B-ALL |
| t(15; 17)(q21-q11-22) | Giliard, E. F. & Solomon, E. Sem. Cancer Biol. 4, 359-368 (1993) | *PML* (15Q21)<br>*RARA* (17q21) | Zinc-finger<br>Retinoic acid receptor-α | Zinc-finger + RAR DNA and ligand binding | APL |
| t(11; 17)(q23; q21.1) | Chen, Z. et al. EMBO J. 12, 1161-1167 (1993) | *PLZF* (11q23)<br>*RARA* (17q21) | Zinc-finger<br>Retinoic acid receptorα | Zn-finger + RAR DNA and ligand binding | APL |
| t(4; 11)(q21; q23) | Djabali, M. et al. Nature Genet. 2, 113-118 (1992); Gu, Y. et al. Cell 71, 701-708 (1992) | *MLL* (11q23)<br>*AF4* (4q21) | A-T hook/Zn-finger<br>Ser-Pro rich | A-T hook + (Ser-pro) | ALL/preB-ALL/ ANLL |
| t(9; 11)(q21; q23) | Nakamura, T. et al. Proc. natn. Acad. Sci. U.S.A. 90, 4631-4635 (1993); Lida, S. et al. Oncogene 8, 3085-3092 (1993) | *MLL* (11q23)<br>*AF9/MLLT3* (9p22) | A-T hook/Zn-finger<br>Ser-Pro rich | A-T hook + (Ser-Pro) | ALL/preB-ALL/ ANLL |
| t(11; 19)(q23; p13) | Tkachuk, D. C., Kohler, S. & Cleary, M. L. Cell 71, 691-700 (1992); Yamamoto, K. et al. Oncogene 8, 2617-2625 (1993) | *MLL* (11q23)<br>*ENL* (19p13) | A-T hook/Zn-finger<br>Ser-Pro rich | A-T hook + Ser-Pro | pre-B-ALL/ T-ALL/ ANLL |



WO 02/069900 PCT/US02/06518

## FIGURE 1 (Cont'd)

| Type of Aberration | Background Literature | Affected Gene(s) | Protein Domain | Fusion Protein | Disease |
|---|---|---|---|---|---|
| t(X; 11)(q13; q23) | Corral, J. et al. Proc. natn. Acad. Sci. U.S.A. 90, 8538-8542 (1993) | *MLL* (11q23)<br>*AFX1* (Zq13) | A-T hook/Zn-finger<br>Ser-Pro rich | A-T hook + (Ser-Pro) | T-ALL |
| t(1; 11)(p32; q23) | Bernard, O. A., Mauchauffe, M., Mecucci, C., Van Den Berghe, H. & Berger, R. Oncogene 9, 1039-1045 (1994) | *MLL* (11q23)<br>*AF1P* (1p32) | A-T hook/Zn-finger<br>Eps-15 homologue | A-T hook + | ALL |
| t(6; 11)(q27; q23) | Prasac, R. et al. Cancer Res. 53, 5624-5628 (1993) | *MLL* (11q23)<br>*AF6* (6q27) | A-T hook/Zn-finger<br>myosin homologue | A-T hook + | ALL |
| t(11; 17)(q23; q21) | Prasac, R. et al. Proc. natn. Acad. Sci. U.S.A. 91, 8107-8111 (1994) | *MLL* (11q23)<br>*AF17* (17q21) | A-T hook/Zn-finger<br>Cys-rich/leucine zipper | A-T hook + leucine zipper | AML |
| t(8; 21)(q22; q22) | Ohki, M. Sem. Cancer Biol. 4, 369-376 (1993) | *AML1/CBFα* (21q22)<br>*ETO/MTG8* (8q22) | DNA binding/runt homology<br>Zn-finger | DNA binding + Zn-fingers | AML |
| t(3; 21)(q26; q22) | Mitani, K. et al. EMBO J. 13, 504-510 (1994) | *AML1* (21q22)<br>*EVI-1* (3q26) | DNA binding<br>Zn-finger | DNA binding + Zn-fingers | CML |
| t(3; 21)(q26; q22) | Nucifora, G., Begy, C. R., Erickson, P., Drackin, H. A. & Rowley, J. D. Proc. natn. Acad. Sci. U.S.A. 90, 7784-7788 (1993) | *AML1* (21q22)<br>*EAP* (3q26) | DNA binding<br>Sn protein | DNA binding<br>+ out-of-frame EAP | Myelo-dyspiasia |
| 5(16; 21)(p11; q22) | Shimizu, K. et al. Proc. natn. Acad. Sci. U.S.A. 90, 10280-10284 (1993) | *FUS* (16p11)<br>*ERG* (21q22) | Gin-Ser Tyr/Gly-rich/RNA binding<br>Ets-like DNA binding | Gin-Ser-Tyr + DNA binding | Myeloid |
| t(6; 9)(p23; q34) | von Lindern, M. et al. Molec. Cell Biol. 12, 1687-1697 (1992) | *DEK* (6p23)<br>*CAN* (9q34) | unkown<br>ZIP | ZIP+ | AML |
| 9; 9? | von Lindern, M., Breems, D., van Baal, S., Acriaansen, H. & Grosveld, G. Genes Chrom. Cancer 5, 227-234 (1992) | *SET* (9q34)<br>*CAN* (9p34) | ZIP | ZIP+ | AUL |
| t(4; 16)(q26; p13) | Laabi, Y. et al. EMBO J. 11, 3897-3904 (1992) | IL-2 (4q26)<br>*BCM* (16p13.1) | IL2<br>TM domain | IL-2/TM | T-lymphoma |

## FIGURE 1 (Cont'd)

| Type of Aberration | Background Literature | Affected Gene(s) | Protein Domain | Fusion Protein | Disease |
|---|---|---|---|---|---|
| inv(2; 2)(p13; p11.2-14) | Lu, D. et al. Oncogene 6, 1235-1241 (1991) | *REL* (2p13)<br>*NRG* (2p11.2-14) | DNA binding-activator not known | DNA binding + | NHL |
| inv(16)(p13q22) | Liu, P. et al. Science 261, 1041-1044 (1993) | Myosin MYH11 (16p13)<br>CBF-$\beta$ (16q22) | | DNA binding? | AML |
| t(5; 12)(q33; p13) | Golub, T. R., Barker, G. F., Lovett, M. & Gilliland, D. G. Cell 77, 307-316 (1994) | PDGF-$\beta$ (5q33)<br>TEL (12p13) | Receptor kinase<br>Ets-like DNA binding | Kinase + DNA binding | CMML |
| t(2; 5)(2p23; q35) | Morris, S. W. et al. Science 263, 1281-1284 (1994) | *NPM* (5q35)<br>*ALK* (2p23) | Nuclear phosphoprotein<br>Tyrosine kinase | N terminus NPM + kinase | NHL |
| t(11; 22)(q24; q12) | Delattre, O. et al. Nature 359, 162-165 (1992) | *FLI1* (11q24)<br>*EWS* (22q12) | Ets-like DNA binding<br>Gln-Ser-Tyr/Gly-rich/RNA binding | Gln-Ser-Tyr + DNA binding | Ewing's sarcoma |
| inv10(q11.2; q21) | Pierotti, M. A. et al. Proc. natn. Acad. Sci. U.S.A. 89, 1616-1620 (1992) | *RET* (10q11.2)<br>*D10S170* (q21) | tyrosine kinase<br>uncharacterized | Unk + tyrosine kinase | Papillary thyroid carcinoma |
| t(12; 22)(q13; q12) | Zucman, J. et al. Nature Genet. 4, 341-345 (1993) | *ATF1* (12q13)<br>*EWS* (22q12) | bZIP<br>Gln-Ser-Tyr/Gly-rich/RNA binding | Gln-Ser-Tyr + bZIP | a melanoma |
| t(12; 16)(q13; p11) | Crozat, A., Aman, P., Mandahl, N. & Ron, D. Nature 363, 640-644 (1993); Rabbitts, T. H. ; Forster, A., Larson, R. & Nathan, P. Nature Genet. 4, 175-180 (1993) | *CHOP* (12q13)<br>*FUS (16p11)* | (DNA binding?)/ZIP<br>Gln-Ser-Tyr/Gly-rich/RNA binding | Gln-Ser-Tyr +(DNA binding?)/ZIP | Liposarcoma |
| t(2; 13)(q35; q14) | Ben-David, Y., Giddens, E. B., Letwin, K. & Bernstein, A. Genes Dev. 5, 908-918 (1991) | *PAX3* (2q35)<br>*FKHR* (13q14) | Paired box/homeodomain<br>Forkhead domain | PB/HD +DNA binding | Rhabdomyosarcoma |
| t(X; 18)(p11.2;q11.2) | Clark, J. et al. Nature Genet. 7, 502-5087 (1994) | *SYT* (18q11.2)<br>*SSX* (Xp11.2) | None identified<br>None identified | | Synovial sarcoma |

SEQUENCE LISTING

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<120> METHODS FOR TREATING GENETICALLY-DEFINED PROLIFERATIVE DISORDERS WITH HSP90 INHIBITORS

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Ala Glu Trp Arg Glu Asn Ile Arg Glu Gln Gln Lys Lys Cys Phe Arg
 65                  70                  75                  80

Ser Phe Ser Leu Ala Ser Val Glu Leu Gln Met Leu Thr Asn Ser Cys
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Val Lys Leu Gln Thr Val His Ser Ile Pro Leu Thr Ile Asn Lys Glu
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Asp Asp Glu Ser Pro Gly Leu Tyr Gly Phe Leu Asn Val Ile Val His
        115                 120                 125

Ser Ala Thr Gly Phe Lys Gln Ser Ser Lys Leu Gln Arg Pro Val Ala
    130                 135                 140

Ser Asp Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala Arg Trp Asn Ser
145                 150                 155                 160

Lys Glu Asn Leu Leu Ala Ala Pro Ser Glu Asn Asp Pro Asn Leu Phe
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Val Ala Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu Ser Ile
            180                 185                 190

Thr Lys Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Asn Gly Glu
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Tyr
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         35                  40                  45

Tyr Glu Arg Ala Glu Trp Arg Glu Asn Ile Arg Glu Gln Gln Lys Lys
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Cys Phe Arg Ser Phe Ser Leu Thr Ser Val Glu Leu Gln Met Leu Thr
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Arg Pro Val Ala Ser Asp Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala
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Arg Trp Asn Ser Lys Glu Asn Leu Leu Ala Gly Pro Ser Glu Asn Asp
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Pro Asn Leu Phe Val Ala Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn
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Thr Leu Ser Ile Thr Lys Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn
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His Asn Gly Glu Trp Cys Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp
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Val Pro Ser Asn Tyr Ile Thr Pro Val Asn Ser Leu Glu Lys His Ser
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Trp Tyr His Gly Pro Val Ser Arg Asn Ala Ala Glu Tyr Leu Leu Ser
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Ser Gly Ile Asn Gly Ser Phe Leu Val Arg Glu Ser Glu Ser Ser Pro
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Tyr Gly Phe Leu Asn Val Ile Val His Ser Ala Thr Gly Phe Lys Gln
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Met Glu Glu Ala Leu Gln Arg Pro Val Ala Ser Asp Phe Glu Pro Gln

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Gly Pro Ser Glu Asn Asp Pro Asn Leu Phe Val Ala Leu Tyr Asp Phe
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Val Ala Ser Gly Asp Asn Thr Leu Ser Ile Thr Lys
    130                 135                 140
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<210> 20
<211> 423
<212> DNA
<213> Homo sapiens

<400> 20
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cacagaactt cctgtccagc atcaatgagg agatcacacc ccgacggcag tccatgacgg 180
tgaagaaggg agagggagaa gacaggatga aagcttcatc aacgaggaag agattactcc 240
ttatggaaga agcccttcag cggccagtag catctgactt tgagcctcag ggtctgagtg 300
aagccgctcg ttggaactcc aaggaaaacc ttctcgctgg acccagtgaa aatgacccca 360
acctttttcgt tgcactgtat gattttgtgg ccagtggaga taacactcta agcataacta 420
aag 423

<210> 21
<211> 307
<212> PRT
<213> Homo sapiens

<400> 21

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Ala Asn Lys Gly Ser Lys Ala Thr Glu Arg Leu Lys Lys Lys Leu Ser
  1               5                  10                  15

Glu Gln Glu Ser Leu Leu Leu Leu Met Ser Pro Ser Met Ala Phe Arg
             20                  25                  30

Val His Ser Arg Asn Gly Lys Ser Tyr Thr Phe Leu Ile Ser Ser Asp
         35                  40                  45

Tyr Glu Arg Ala Glu Trp Arg Glu Asn Ile Arg Glu Gln Gln Lys Lys
     50                  55                  60

Cys Phe Arg Ser Phe Ser Leu Thr Ser Val Glu Leu Gln Met Leu Thr
 65                  70                  75                  80

Asn Ser Cys Val Lys Leu Gln Thr Val His Ser Ile Pro Leu Thr Ile
                85                  90                  95

Asn Lys Glu Glu Ala Leu Gln Arg Pro Val Ala Ser Asp Phe Glu Pro
            100                 105                 110

Gln Gly Leu Ser Glu Ala Ala Arg Trp Asn Ser Lys Glu Asn Leu Leu
        115                 120                 125
```

```
Ala Gly Pro Ser Glu Asn Asp Pro Asn Leu Phe Val Ala Leu Tyr Asp
    130                 135                 140

Phe Val Ala Ser Gly Asp Asn Thr Leu Ser Ile Thr Lys Gly Glu Lys
145                 150                 155                 160

Leu Arg Val Leu Gly Tyr Asn His Asn Gly Glu Trp Cys Glu Ala Gln
                165                 170                 175

Thr Lys Asn Gly Gln Gly Trp Val Pro Ser Asn Tyr Ile Thr Pro Val
            180                 185                 190

Asn Ser Leu Glu Lys His Ser Trp Tyr His Gly Pro Val Ser Arg Asn
        195                 200                 205

Ala Ala Glu Tyr Leu Leu Ser Ser Gly Ile Asn Gly Ser Phe Leu Val
    210                 215                 220

Arg Glu Ser Glu Ser Ser Pro Gly Gln Arg Ser Ile Ser Leu Arg Tyr
225                 230                 235                 240

Glu Gly Arg Val Tyr His Tyr Arg Ile Asn Thr Ala Ser Asp Gly Lys
                245                 250                 255

Leu Tyr Val Ser Ser Glu Ser Arg Phe Asn Thr Leu Ala Glu Leu Val
            260                 265                 270

His His His Ser Thr Val Ala Asp Gly Leu Ile Thr Thr Leu His Tyr
        275                 280                 285

Pro Ala Pro Lys Arg Asn Lys Pro Thr Val Tyr Gly Val Ser Pro Asn
    290                 295                 300

Tyr Asp Lys
305
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<210> 22
<211> 922
<212> DNA
<213> Homo sapiens

<400> 22

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tacacgttcc tgatctcctc tgactatgag cgtgcagagt ggagggagaa catccgggag 180
cagcagaaga agtgtttcag aagcttctcc ctgacatccg tggagctgca gatgctgacc 240
aactcgtgtg tgaaactcca gactgtccac agcattccgc tgaccatcaa taaggaagaa 300
gcccttcagc ggccagtagc atctgacttt gagcctcagg gtctgagtga agccgctcgt 360
tggaactcca aggaaaacct tctcgctgga cccagtgaaa atgaccccaa ccttttcgtt 420
gcactgtatg attttgtggc cagtggagat aacactctaa gcataactaa aggtgaaaag 480
ctccgggtct taggctataa tcacaatggg gaatggtgtg aagcccaaac caaaaatggc 540
caaggctggg tcccaagcaa ctacatcacg ccagtcaaca gtctggagaa acactcctgg 600
taccatgggc ctgtgtcccg caatgccgct gagtatctgc tgagcagcgg gatcaatggc 660
agcttcttgg tgcgtgagag tgagagcagt cctggccaga ggtccatctc gctgagatac 720
gaagggaggg tgtaccatta caggatcaac actgcttctg atggcaagct ctacgtctcc 780
tccgagagcc gcttcaacac cctggccgag ttggttcatc atcattcaac ggtggccgac 840
gggctcatca ccacgctcca ttatccagcc ccaaagcgca acaagcccac tgtctatggt 900
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gtgtccccca actacgacaa gt 922

<210> 23
<211> 359
<212> PRT
<213> Homo sapiens

<400> 23

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Tyr Gln Pro Tyr Gln Ser Ile Tyr Val Gly Gly Met Met Glu Gly Glu
  1               5                  10                  15

Gly Lys Gly Pro Leu Leu Arg Ser Gln Ser Thr Ser Glu Gln Glu Lys
             20                  25                  30

Arg Leu Thr Trp Pro Arg Arg Ser Tyr Ser Pro Arg Ser Phe Glu Asp
         35                  40                  45

Cys Gly Gly Gly Tyr Thr Pro Asp Cys Ser Ser Asn Glu Asn Leu Thr
     50                  55                  60

Ser Ser Glu Glu Asp Phe Ser Ser Gly Gln Ser Ser Arg Val Ser Pro
 65                  70                  75                  80

Ser Pro Thr Thr Tyr Arg Met Phe Arg Asp Lys Ser Arg Ser Pro Ser
                 85                  90                  95

Gln Asn Ser Gln Gln Ser Phe Asp Ser Ser Ser Pro Pro Thr Pro Gln
            100                 105                 110

Cys His Lys Arg His Arg His Cys Pro Val Val Val Ser Glu Ala Thr
        115                 120                 125

Ile Val Gly Val Arg Lys Thr Gly Gln Ile Trp Pro Asn Asp Gly Glu
    130                 135                 140

Gly Ala Phe His Gly Asp Ala Glu Ala Leu Gln Arg Pro Val Ala Ser
145                 150                 155                 160

Asp Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala Arg Trp Asn Ser Lys
                165                 170                 175

Glu Asn Leu Leu Ala Gly Pro Ser Glu Asn Asp Pro Asn Leu Phe Val
            180                 185                 190

Ala Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu Ser Ile Thr
        195                 200                 205

Lys Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Asn Gly Glu Trp
    210                 215                 220

Cys Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp Val Pro Ser Asn Tyr
225                 230                 235                 240

Ile Thr Pro Val Asn Ser Leu Glu Lys His Ser Trp Tyr His Gly Pro
                245                 250                 255

Val Ser Arg Asn Ala Ala Glu Tyr Leu Leu Ser Ser Gly Ile Asn Gly
```

260 265 270

Ser Phe Leu Val Arg Glu Ser Glu Ser Ser Pro Gly Gln Arg Ser Ile
275 280 285

Ser Leu Arg Tyr Glu Gly Arg Val Tyr His Tyr Arg Ile Asn Thr Ala
290 295 300

Ser Asp Gly Lys Leu Tyr Val Ser Ser Glu Ser Arg Phe Asn Thr Leu
305 310 315 320

Ala Glu Leu Val His His His Ser Thr Val Ala Asp Gly Leu Ile Thr
325 330 335

Thr Leu His Tyr Pro Ala Pro Lys Arg Asn Lys Pro Thr Val Tyr Gly
340 345 350

Val Ser Pro Asn Tyr Asp Lys
355

<210> 24
<211> 1079
<212> DNA
<213> Homo sapiens

<400> 24
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ctactccccc cggagttttg aggattgcgg aggcggctat accccggact gcagctccaa 180
tgagaacctc acctccagcg aggaggactt ctcctctggc cagtccagcc gcgtgtcccc 240
aagccccacc acctaccgca tgttccggga caaaagccgc tctccctcgc agaactcgca 300
acagtccttc gacagcagca gtcccccccac gccgcagtgc cataagcggc accggcactg 360
cccggttgtc gtgtccgagg ccaccatcgt gggcgtccgc aagaccgggc agatctggcc 420
caacgatggc gagggcgcct tccatggaga cgcagaagcc cttcagcggc cagtagcatc 480
tgactttgag cctcagggtc tgagtgaagc cgctcgttgg aactccaagg aaaaccttct 540
cgctggaccc agtgaaaatg accccaacct tttcgttgca ctgtatgatt ttgtggccag 600
tggagataac actctaagca taactaaagg tgaaaagctc cgggtcttag gctataatca 660
caatggggaa tggtgtgaag cccaaaccaa aaatggccaa ggctgggtcc caagcaacta 720
catcacgcca gtcaacagtc tggagaaaca ctcctggtac catgggcctg tgtcccgcaa 780
tgccgctgag tatctgctga gcagcgggat caatggcagc ttcttggtgc gtgagagtga 840
gagcagtcct ggccagaggt ccatctcgct gagatacgaa gggagggtgt accattacag 900
gatcaacact gcttctgatg gcaagctcta cgtctcctcc gagagccgct tcaacaccct 960
ggccgagttg gttcatcatc attcaacggt ggccgacggg ctcatcacca cgctccatta 1020
tccagcccca aagcgcaaca agcccactgt ctatggtgtg tcccccaact acgacaagt 1079

<210> 25
<211> 34
<212> PRT
<213> Homo sapiens

<400> 25
Val Gly Val Arg Lys Thr Gly Gln Ile Trp Pro Asn Asp Gly Glu Gly
1 5 10 15

Ala Phe His Gly Asp Ala Gly Lys Ser Pro Gly Leu Arg Leu Asn His
20 25 30